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(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: MESENS, Jean, Louis [BE/BE]; Moereind 17, B-2275 Wechelderzande (BE).

(74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).

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(54) Title: RATE-CONTROLLED TRANSDERMAL ADMINISTRATION OF RISPERIDONE

(57) Abstract

Medical patches for the rate-controlled transdermal administration of risperidone through intact skin for an extended period of time which comprise: (a) a drug reservoir (1) comprising risperidone (I) and a skin permeation enhancer (II) for risperidone in amounts sufficient to deliver (I) at a therapeutically effective rate for said extended period of time, and (b) a drug-impermeable backing (2); methods of treating patients with such patches; process of manufacturing such patches.

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RATE-CONTROLLED TRANSDERMAL ADMINISTRATION OF RISPERIDONE

This invention relates to a medical patch for the rate-controlled transdermal administration of risperidone and to a method of treating a subject by administering risperidone thereto with said medical patch.

Risperidone is generic to 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. The preparation and pharmacological activity thereof are described in U.S. Pat. No. 4,804,663 [corresponding to EP-0,196,132 (1984)]. Various conventional pharmaceutical dosage forms, including tablets, capsules, drops, suppositories, oral solutions and injectable solutions are exemplified therein. In practice, risperidone will normally be administered as the base in a tablet or in a buffered, oral or intramuscular solution for the purposes of producing an antipsychotic effect or alleviating behavioral disturbances associated with neurodegenerative disorders. For a number of reasons, it is desirable to administer risperidone in a rate-controlled manner using a non-invasive route, in particular using transdermal delivery.

The application of transdermal drug delivery technology to the administration of a wide variety of drugs has been proposed and various systems for accomplishing this are disclosed in numerous technical journals, handbooks and patents. These systems can deliver controlled amounts of drugs to patients for extended periods of time ranging in duration from several hours to several days. So far there are no patents nor is there any other prior art that describes a transdermal delivery system which is intended to deliver risperidone. Nor are there data on skin permeability or therapeutic transdermal delivery rates of risperidone adequate to design such a system. In addition, risperidone has characteristics which impose a combination of restraints on a transdermal delivery system which have hitherto not been addressed in other systems.

Risperidone is a highly potent drug having a relatively narrow therapeutic index. It may produce undesirable side effects on overdosage, most notably extra pyramidal syndrome (EPS) and to a lesser extent hypotension (due to peripheral alpha-adrenergic activity). For the purpose of producing an antipsychotic effect in a patient the total daily dose of risperidone ranges from about 2 to about 8 mg ; for the alleviation of behavioral disturbances associated with neurodegenerative disorders the total daily dose is usually less and typically ranges from about 0.5 to about 2 mg. Inter-individual differences and additional medication may necessitate dose titrating in patients.

Risperidone is metabolized to 9-hydroxyrisperidone which has a pharmacological profile and potency comparable with that of the parent drug risperidone, but which has a longer elimination half-life. Risperidone is distributed to and eliminated from the brain tissues more rapidly than its metabolite 9-hydroxyrisperidone.

In the metabolism of risperidone, debrisoquine-type genetic polymorphism plays a distinct role. As a consequence, humans can be phenotyped as poor, intermediate or extensive metabolizers on the basis of their metabolic ratio. Said metabolic ratio is defined as the ratio of urine recovery of debrisoquine to that of the 4-hydroxymetabolite of debrisoquine over a period of 8 hours after an oral intake of 10 mg debrisoquine. In oriental people more than 99% of the population can be phenotyped as extensive metabolizers and poor metabolizers are rather seldom. In the Caucasian race however only about 90% of the population can be phenotyped as either extensive or intermediate metabolizers. Approximately 10% of the population are poor metabolizers and have deficient amounts of the debrisoquine-hydroxylase enzyme.

The duration of action and the peak plasma levels of active agents (risperidone and 9-hydroxyrisperidone) is very dependent on the debrisoquine metabolic rate of the human subject treated with risperidone. More in particular, in poor metabolizers high transient peak levels of risperidone are likely to be attained when the total daily amount is administered in a single dose. This may give rise to undesired side-effects such as extra pyramidal syndrome (EPS) and hypotension (due to the adrenergic effect).

Further inter-individual differences among humans, as far as the metabolism of risperidone is concerned, are due to the fact that in clinical practice the human subjects to be treated with risperidone will usually receive additional medication, e.g. tranquillizers such as phenothiazines, neuroleptica such as haloperidol, antidepressiva etc., all of which will compete with risperidone for the debrisoquine-hydroxylase enzyme. These drug interactions may seriously affect the metabolism of risperidone, especially in extensive metabolizers, and may result in the occurrence of adverse effects in patients receiving such additional medication.

In general, the rapid distribution of risperidone both in plasma and in brain tissues, indicates that the drug can better be administered in divided doses at regular intervals and can best be administered at a continuous controlled rate so as to avoid excessive peak levels (and the possibility of side-effects) while at the same time maintaining clinically effective drug levels. A rate-controlled transdermal delivery system clearly would offer a

practical solution to the above, provided that risperidone can be administered percutaneously.

Further, it would be desirable that the device delivers the drug at a substantially constant rate for at least about 24 hours while at the same time keeping the amount of drug within both the unused and depleted systems to a minimum. Also, the degree to which the system controls the release rate should be relatively high in order to assure that excessive amounts of the drug are not delivered in the event that the skin of a patient has been damaged, has an abnormally high permeability, or the patient is a poor metabolizer. On the other hand, the release rate per unit area of system cannot be selected at such a low level that the onset of an antipsychotic effect is delayed or that adequate dosages are not obtained from reasonably sized systems. In addition to these general design criteria, properties of risperidone such as skin permeability and drug binding in the skin may impose additional conflicting design constraints.

Given risperidone's pharmacological profile, the delivery of risperidone in therapeutic amounts for continuous periods from transdermal systems which rely primarily on skin permeability to control drug input rate, is impossible. It is necessary to deliver the drug from a rate-controlled transdermal system in which the system itself controls the maximum rate at which the drug is delivered through the skin.

Interestingly, it has now been found that risperidone in the presence of a suitable skin permeation enhancer (SPE) can be administered through intact skin at a rate which is sufficient to attain therapeutically meaningful plasma and brain tissue levels. Consequently, the present invention concerns a medical patch for the rate-controlled transdermal administration of risperidone through intact skin for an extended period of time which comprises :

(a) a drug reservoir (1) comprising risperidone (I) and a skin permeation enhancer (II) for risperidone in amounts sufficient to deliver (I) at a therapeutically effective rate for said extended period of time, and
(b) a drug-impermeable backing (2).

The invention also concerns a method for inducing and maintaining an antipsychotic effect or for alleviating behavioral disturbances associated with neurodegenerative disorders, which comprises administering risperidone through an area of intact skin at a therapeutically effective rate for an extended period of time with a medical patch as described herein.

There is a relatively wide range of permeability of normal human skin to risperidone and this permeability not only varies from individual to individual and site to site but is also highly dependent on the chemical form of the drug. We have discovered that risperidone in a buffered solution, the form in which risperidone is presented for oral and intramuscular administration, has such a low skin permeability that it is not at all suitable for transdermal delivery, even with the use of skin permeation enhancers. Instead, in order to obtain the delivery rates noted above, the drug should be incorporated in the transdermal therapeutic system in the uncharged form of the base. Consequently, the term risperidone as used hereinafter comprises the base form and other uncharged forms such as its solvates, e.g. its hydrates.

The permeability of normal skin to risperidone base is rather low and an amount of permeation enhancer should be provided in a rate-controlled system sufficient to increase the flux of drug through the skin to a value no less than the flux of drug from the system. Thus, sufficient permeation enhancer should be delivered to increase the permeability of even the most impermeable skin to a value at least equal to that of the patch. This will produce a patch in which at least 50% of the flux is controlled by the patch. It is preferable that the patch be at least 70% controlling and this objective can be obtained if the permeability of skin for the drug is increased to at least 2.4 times the steady state flux from the patch.

Suitable skin penetration enhancers induce a temporary, reversible increase in skin permeability. The skin permeation enhancer (II) to be used in the risperidone patches according to the present invention is selected from the group consisting of fatty acids, monoglyceride esters of such fatty acids, C_{8-18} alkylsaccharides, C_{8-18} acyl carnitines, azone (1-dodecylazacycloheptan-2-one) and C_{1-14} alkyl methylsulfoxides. Fatty acids are saturated and unsaturated C_{8-20} alkanoic acids such as caprylic ($C_{8:0}$), capric ($C_{10:0}$), lauric ($C_{12:0}$), myristic ($C_{14:0}$), palmitic ($C_{16:0}$), palmitoleic ($C_{16:1}$), stearic ($C_{18:0}$), oleic ($C_{18:1}$), linoleic ($C_{18:2}$), linolenic ($C_{18:3}$), and arachidonic ($C_{20:4}$) acid. C_{8-18} alkylsaccharides are for example n-octyl-beta-D-glucopyranoside and n-lauryl-beta-D-glycopyranoside. C_{1-14} alkyl methylsulfoxides are for example dimethyl-sulfoxide and decyl methysulfoxide. Preferred are the saturated C_{8-14} alkanoic acids and the unsaturated C_{16-20} alkanoic acids having cis double bonds, especially lauric acid and oleic acid. The skin permeation enhancer (II) should be used in an amount that does not damage the skin of the subject to be treated; in practice this means that the weight-by-weight ratio (I) : (II) in the patches ranges from 10:1 to 1:10 and in particular is from about 1:1 to about 1:5 in the case of the especially preferred lauric acid and oleic acid.

Risperidone in the presence of a skin permeation enhancer thus may be administered to the human body via the transdermal route at a therapeutically effective rate for an extended period of time : a rate in the range of 10 to 400 μg/h for a substantial portion of said extended period of time is feasible. Steady-state administration rates obtainable range from about 10-300 μg/h and preferably from about 25-150 μg/h.

When transdermal systems according to this invention are applied to the skin, the drug will be transferred from the system into the skin where it is absorbed into the bloodstream to produce its systemic antipsychotic effect. The skin contains risperidone binding sites which must be saturated before any significant absorption into the bloodstream occurs. The initial saturation of these sites should proceed rapidly in order to provide rapid onset of an antipsychotic effect. Since most transdermal therapeutic systems exhibit an initial transitory, increased release of drug which occurs at a significantly higher rate than the steady-state rate later obtained, inclusion of additional amounts of the drug at the skin contacting surface of the device is not an absolute requirement. The systems described herein should be capable of delivering drug at initial rates which should induce the onset of an antipsychotic effect within from four to eight hours after application.

The skin binding sites are significant in establishing an upper limit on the size of the transdermal therapeutic system and, conversely, the lower limit on the usable delivery rate. The total amount of drug contained in the binding sites is directly proportional to the surface area of the delivery system and is independent of the rate at which the drug is delivered. When such a system is removed the total amount of bound drug must be absorbed by the body before the action of the drug stops. In view of the high potency of risperidone it is preferable that the amount of drug solubilized in the skin be maintained at or below 0.5 to 1 mg level to permit prompt termination of therapy.

A suitable patch according to the present invention delivers risperidone through about 5-100 cm^2 and preferably about 10-50 cm^2, especially about 20 cm^2 of intact skin over an extended period of time, and at a rate within the range of about 0.5 to 20 $\mu g/cm^2.h$ and preferably at a rate within the range of approximately 1-5 $\mu g/cm^2.h$. When so delivered it is possible, by appropriate selection of the surface area of the drug delivery device to obtain total drug input rates which provide an adequate range of titration for individual patient needs while maintaining a safe and effective dosage form. A suitable patch according to the present invention comprises sufficient (I) and (II) to allow administration for up to 4 days. A 1 to 3 day regimen is considered preferable.

When a prolonged antipsychotic effect is desired, the depleted patch is removed and a fresh system applied to a new location. Since saturation of the skin binding sites usually occurs at substantially the same rate as absorption of bound drug, blood levels will remain substantially constant.

Having described the requirements imposed on transdermal therapeutic systems for administering the base form of risperidone and methods for its transdermal administration, the following description concerns various specific rate-controlled transdermal patch designs. Figures 1 to 5 are all cross-sectional views of such patches.

A first type of rate-controlled transdermal patch is shown in Figure 1 : a polymer membrane permeation-controlled patch wherein the drug reservoir (1) is sandwiched between the drug-impermeable backing (2) and a rate-controlling polymeric membrane (4) on the external surface of which a layer (3) of an adhesive polymer is applied. The rate-controlling polymeric membrane (4) has a specific permeability and may be made of a nonporous (homogeneous or heterogeneous) polymeric material or of a porous (semipermeable) membrane.

The drug reservoir (1) may exist in solid, suspension or solution form. Preferably, the drug reservoir (1) contains :

(i) a suspension comprising (I) and (II) dispersed homogeneously in a solid polymer matrix suspended in a liquid medium, [e.g. polisobutylene in silicone fluid] or
(ii) a drug solution comprising (I) and (II) in a releasable solvent [e.g. alkyl alcohols and diols such as ethanol, 1-propanol, 1-butanol, 1-octanol, lauryl alcohol, linolenyl alcohol, and propylene glycol]. The releasable solvents may have skin permeation enhancing properties for risperidone by themselves, e.g. propylene glycol. Therefore, the drug solution comprises in particular propylene glycol as a releasable solvent.

A patch wherein the drug reservoir (1) contains a solution comprising 0.1 to 10% by weight of (I), 0.1 to 10% by weight of (II), and propylene glycol ad 100 % is presently considered the formula of choice for insertion in a transdermal delivery system as shown in Fig. 1.

The drug-impermeable backing (2) is preferably a plastic laminate, e.g. a polyester film laminate or a polyester-polyurethane film (which is air and water permeable). Preferably it is flexible and it may be metalized. In order to obtain a system wherein the flux is controlled by the system itself and not just by the permeability of the skin, the rate-

controlling polymeric membrane (4) limits the flux of (I) and (II) from the drug reservoir to a level less than the flux of (I) and (II) through the skin to which it is applied.

In order to minimize the amount of skin permeation enhancer delivered to the patient, it is advantageous that patch has a polymeric membrane (4) which restricts the flux of (I) from the drug reservoir (1) substantially more than the flux of (II) from the drug reservoir (1).

The rate-controlling membrane can be from about 0.5-5 mm thick and preferably about 1-3 mm thick. It can be conveniently made of ethylene-vinyl acetate copolymer (EVA), a polyvinyl acetate or polypropylene. To provide adequate system life, the loading will be from about 5-50 mg/cm^2 yielding a dry loading of from about 0.01-5 mg/cm^2.

The adhesive layer (3) comprises a drug-compatible, hypoallergenic pressure-sensitive adhesive polymer and may be disposed in the flow path of (I) and (II) from the drug reservoir (1) to the skin. Silicone adhesive, polyacrylate, polyisobutylene, are considered particularly useful. However, other means for maintaining this system (and the following designs) on the skin can be employed. Such means include a peripheral ring of adhesive outside the path of drug from the system to the skin, in which case the adhesive need not be drug compatible. The use of adhesive overlays or other fastening means such as buckles, belts, and elastic arm bands is also contemplated.

The drug formulation inside the reservoir can be introduced by injection molding, spray coating, microencapsulation and other techniques known in the art. The rate of drug release from the polymer membrane permeation-controlled system should be constant. The release of drug from this type of rate-controlled drug delivery system is controlled by appropriately choosing the partition coefficient and diffusivity of the drug and the thickness and nature of the rate-controlling polymeric membrane (4).

A second type of rate-controlled patch is shown in Figure 2 : a polymer matrix dif-fusion-controlled patch wherein the drug reservoir (1) comprises a matrix of a hydro-philic or lipophilic polymer wherein (I) and (II) are homogeneously dispersed, said drug reservoir (1) being mounted onto an occlusive baseplate (5) in a compartment fabricated from the drug-impermeable backing (2), and wherein the adhesive layer (3) is applied along the circumference of the patch to form a strip of adhesive rim surrounding the drug reservoir (1). The medicated polymer is formed by homogeneously dispersing (I), (II) and polymer. It is then shaped into a form having a defined surface area and controlled thickness, which form is then mounted onto the occlusive baseplate (5). At steady state the release is continuous, but not constant as the amount of drug delivered is proportional with the square root of the period of time. In this type of patch, the release of drug is

controlled by appropriately choosing the loading dose and the polymer. An absorbent pad (6) can be sandwiched between (2) and (5).

The drug reservoir can also be formulated by directly dispersing the drug in a pressure-sensitive adhesive polymer such as poly(isobutylene)- or a poly(acrylate)-based adhesive polymer. The medicated adhesive polymer is then attached to the drug-impermeable backing to form a single layer or multiple layers of drug reservoir. A patch design of this type is shown in Figure 3 : a polymer matrix diffusion-controlled patch wherein the drug reservoir (1) comprises a pressure-sensitive adhesive polymer wherein (I) and (II) are homogeneously dispersed. A strippable backing member (7) or release liner, preferably siliconized, adapted to be removed prior to use is advantageously used to cover the drug reservoir prior to use.

Figure 4 shows a modification of the previous design : a polymer matrix gradient-controlled patch according to claim 1 wherein the drug reservoir (1) comprises multi-laminate adhesive layers of a pressure-sensitive adhesive polymer wherein (I) and (II) are dispersed in a proportional manner thus forming a concentration gradient which raises from the skin contacting surface towards the drug-impermeable layer (2). The increasing drug loading level of the layers compensates for the increase in diffusional path and under appropriate circumstances a constant drug release profile can be obtained. Alternatives to this approach consist of varying the polymer solubility of the impregnated drug or varying the particle size distribution of drug crystals in the various laminates of the adhesive matrix.

Figure 5 shows a fourth type of design : a microreservoir partition-controlled patch wherein the drug reservoir (1) comprises a matrix of a hydrophilic or lipophilic polymer wherein many discrete, unleachable, microscopic drug reservoirs comprising (I) and (II) are homogeneously dispersed, said drug reservoir (1) being mounted onto an occlusive baseplate (5) in a compartment fabricated from the drug-impermeable backing (2), and wherein the adhesive layer (3) is applied along the circumference of the patch to form a strip of adhesive rim surrounding the drug reservoir (1). The drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-miscible drug solubilizer, and then homogeneously dispersing the drug suspension in a lipophilic polymer by high shear mechanical force to form a multitude of unleachable, microscopic drug reservoirs. The thermodynamically unstable dispersion is fixed by immediately crosslinking the polymer chains in situ. In this type of patch, the release of drug can follow either a partition-controlled or matrix diffusion-controlled process depending on the solubilities of the drug in the liquid compartments and in the polymer matrix.

Such a system has the advantage of being easily fabricated, but in the absence of a rate controlling membrane, delivers drug at a rate which is determined primilarily by the permeability of the skin at the site of application on the particular individual. Thus, while this system can be employed to provide drug delivery rates within the ranges described herein, the actual delivery rate cannot be as precisely controlled as would be with the systems described generally in Fig. 1. Suitable materials for fabricating of the contact adhesive/reservoir layer include EVA polymers having up to 18% vinylacetate content and polyisobutylene/mineral oil containing from 15 to 25% high molecular weight polyisobutylene (e.g., an average molecular weight 1,200,000) 20 to 30% low molecular weight polyisobutylene (e.g. average molecular weight 35,000) and balance of light mineral oil having a viscosity at 38°C. of approximately 10 mPa.s (centipoise). In addition to the drug, the drug reservoir-contact adhesive layer can also contain additives, permeation enhancers and other materials as are generally known to the art.

The drug reservoirs described above may comprise further ingredients. In order to prevent the growth of micro-organisms such as bacteria, yeasts and fungi in the patches, a preservative agent may be added. Suitable preservatives should be physicochemically stable and effective in the circumstances mentioned above. They comprise benzoic acid, sorbic acid, methylparaben, propylparaben, imidazolidinyl urea (= Germall 115®) and diazolidinyl urea (= Germall II®), phenoxetol, benzyl alcohol, quaternary compounds, e.g. benzylalkonium chloride, and the like. The concentration of the preservatives may range from 0.05% to 1%, particularly from 0.1% to 0.5%, and most particularly is about 0.2%.

The drug reservoir may also be sterilized following art-known procedures. Drug reservoirs may be sterilized by irradiation with gamma rays. Drug solutions can be filtered aseptically and then sterilized by autoclaving.

The patches optionally may include additional ingredients known in the art of formulation such as stabilizers (EDTA) , antioxidants (BHT, BHA), solubility enhancers (cyclodextrins), viscosity regulating agents, surfactants (especially non-ionic), hydrating agents (urea), plasticizers (isopropyl myristate) and the like ingredients.

In order for the residual drug in depleted systems to be minimized, we have discovered that the initial concentration of the risperidone in the matrix material should be selected such that it is less than 1 mg/cm^2. For this reason reservoir systems which permit unit

activity to be achieved at low concentrations are presently considered preferable according to our invention.

Several patents describe a wide variety of materials which can be used for fabricating the various layers of the transdermal risperidone delivery systems according to this invention. This invention therefore contemplates the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

The following examples are intended to illustrate the scope of the present invention in all its aspects; all percentages are by weight unless otherwise noted.

Experimental Part : *In vitro* study of the transdermal permeation of risperidone.
An *in vitro* model using a vertical, two-compartment diffusion cell assembly mounted with freshly excised full thickness abdominal skin of hairless rats (Iffa credo) was used in this study. The donor solutions had a volume of 1.5 ml and comprised risperidone, H^3-risperidone (1μCi/ml), solvent and permeation enhancer. The receptor solution in all experiments consisted of Hank's Balanced Salt Solution (Gibco BRL) with sodium azide). The skin permeation profile was followed for up to 50 h by sampling the receptor solution and assaying the drug concentration by measuring the radioactivity (Ready Safe, Beckmann-Wallac 1410LKB). The ratio of the cumulated quantities detected in the receptor compartment to the skin area (ng/cm^2) were plotted in function of the time and the flux of risperidone through the skin in the presence of various solvents and skin permeation enhancers was deduced from the linear part of the plotted results.

Experiment 1 : borate buffer pH 10, 0.1 M + risperidone at 40mg/ml
flux : 0.181μg/cm^2.h
latency period : not determined

Experiment 2 : borate buffer pH 10, 0.1 M (900 μl/ml) + ethanol (95%; 100 μl/ml) + risperidone (100 μg/ml)
flux : 0.869 μg/cm^2.h
latency period : 13.9 h

Experiment 3 : propylene glycol + eucalyptus oil (0%, 1%, 5%) + risperidone 10 mg/ml
flux (0%) : 3.89 μg/cm^2.h
flux (1%) : 4.54 μg/cm^2.h
flux (5%) : 126.74 μg/cm^2.h

latency period (0%) : 14.2 h
latency period (LA %) : 15.2 h
latency period (5%) : 6.2 h

Experiment 4 : propylene glycol + oleic acid (OA) or lauric acid (LA) (0%, 5%) + risperidone 10 mg/ml
flux (0%) : 3.89 µg/cm^2.h
flux (5% OA) : 18.9 µg/cm^2.h
flux (5% LA) : 15.39 µg/cm^2.h
latency period (0%) : 14.2 h
latency period (5% OA) : 17 h
latency period (5% LA) : 4.3 h

From these results one can draw several conclusions

1. Risperidone permeation from a borate buffer with or without ethanol is too low to be of practical value.
2. Risperidone permeation from propylene glycol is decidedly larger than the previous. The very high flux with 5% eucalyptus oil as skin permeation enhancer probably is due to skin damage.
3. Oleic and lauric acid each enhance the transdermal permeation of risperidone from propylene glycol in such a manner that it should be feasible to deliver meaningful doses of risperidone (say from 0.5 to 8 mg/day) in a reasonably sized patch (about 20 cm^2).

Example 1

10 g of risperidone and 50 g of oleic acid is dissolved in 100 ml propylene glycol by stirring. This solution is added to an aqueous acrylate adhesive dispersion while mixing. An adhesive thickener is added and the resulting mixture is stirred until homogenous. Then, the mixture is coated on an impermeable backing such as a polyester film laminate and dried. A release liner (e.g. a siliconized plastic sheet) is laminated to the adhesive layer. The final sheet is die cut to form transdermal devices of about 20 cm^2 comprising about 20 mg risperidone, each of which is packaged individually.

Claims

1. A medical patch for the rate-controlled transdermal administration of risperidone through intact skin for an extended period of time which comprises :
   (a) a drug reservoir (1) comprising risperidone (I) and a skin permeation enhancer (II) for risperidone in amounts sufficient to deliver (I) at a therapeutically effective rate for said extended period of time, and
   (b) a drug-impermeable backing (2).

2. A patch according to claim 1 wherein the skin permeation enhancer (II) is selected from the group consisting of fatty acids, monoglyceride esters of fatty acids, C_{8-18} alkylsaccharides, C_{8-18} acylcarnitines, azone and C_{1-14} alkyl methylsulfoxides.

3. A patch according to claim 2 wherein (I) is delivered through intact skin at a rate in the range of 10 to 400 µg/h for a substantial portion of said extended period of time.

4. A patch according to claim 2 wherein the area of said intact skin is within the range of 5 to 100 cm^2.

5. A patch according to claim 2 wherein (I) is delivered through intact skin at a rate in the range of 0.5 to 20 $\mu g/h.cm^2$.

6. A patch according to claim 2 comprising sufficient (I) and (II) to allow administration of (I) for up to 4 days.

7. A polymer membrane permeation-controlled patch according to claim 1 wherein the drug reservoir (1) is sandwiched between the drug-impermeable backing (2) and a rate-controlling polymeric membrane (4) on the external surface of which a layer (3) of an adhesive polymer is applied.

8. A patch according to claim 7 wherein the drug reservoir (1) contains
   (i) a suspension comprising (I) and (II) dispersed homogeneously in a solid polymer matrix suspended in a liquid medium, or
   (ii) a drug solution comprising (I) and (II) in a releasable solvent.

9. A patch according to claim 8 wherein the drug solution comprises propylene glycol as a releasable solvent.

10. A patch according to claim 9 wherein the drug reservoir (1) contains a solution comprising 0.1 to 10% by weight of (I), 0.1 to 10% by weight of (II), and

propylene glycol ad 100 %.

11. A patch according to claim 7 wherein the rate-controlling polymeric membrane (4) is either a porous polymeric membrane or a nonporous polymeric membrane.

12. A patch according to claim 11 wherein the rate-controlling polymeric membrane (4) limits the flux of (I) and (II) from the drug reservoir to a level less than the flux of (I) and (II) through the skin to which it is applied.

13. A patch according to claim 11 wherein the polymeric membrane (4) restricts the flux of (I) from the drug reservoir (1) substantially more than the flux of (II) from the drug reservoir (1).

14. A patch according to claim 7 wherein the adhesive layer (3) is disposed in the flow path of (I) and (II) from the drug reservoir (1) to the skin.

15. A polymer matrix diffusion-controlled patch according to claim 1 wherein the drug reservoir (1) comprises a matrix of a hydrophilic or lipophilic polymer wherein (I) and (II) are homogeneously dispersed, said drug reservoir (1) being mounted onto an occlusive baseplate (5) in a compartment fabricated from the drug-impermeable backing (2), and wherein the adhesive layer (3) is applied along the circumference of the patch to form a strip of adhesive rim surrounding the drug reservoir (1).

16. A polymer matrix diffusion-controlled patch according to claim 1 wherein the drug reservoir (1) comprises a pressure-sensitive adhesive polymer wherein (I) and (II) are homogeneously dispersed.

17. A polymer matrix gradient-controlled patch according to claim 1 wherein the drug reservoir (1) comprises multilaminate adhesive layers of a pressure-sensitive adhesive polymer wherein (I) and (II) are dispersed in a proportional manner thus forming a concentration gradient which raises from the skin contacting surface towards the drug-impermeable layer (2).

18. A microreservoir partition-controlled patch according to claim 1 wherein the drug reservoir (1) comprises a matrix of a hydrophilic or lipophilic polymer wherein many discrete, unleachable, microscopic drug reservoirs comprising (I) and (II) are homogeneously dispersed, said drug reservoir (1) being mounted onto an occlusive baseplate (5) in a compartment fabricated from the drug-impermeable backing (2), and wherein the adhesive layer (3) is applied along the circumference of the patch to form a strip of adhesive rim surrounding the drug reservoir (1).

19. A method for inducing and maintaining an antipsychotic effect or for alleviating behavioral disturbances associated with neurodegenerative disorders, which comprises administering risperidone through an area of intact skin at a therapeutically effective rate for an extended period of time with a medical patch as claimed in any one of the claims 1 to 18.

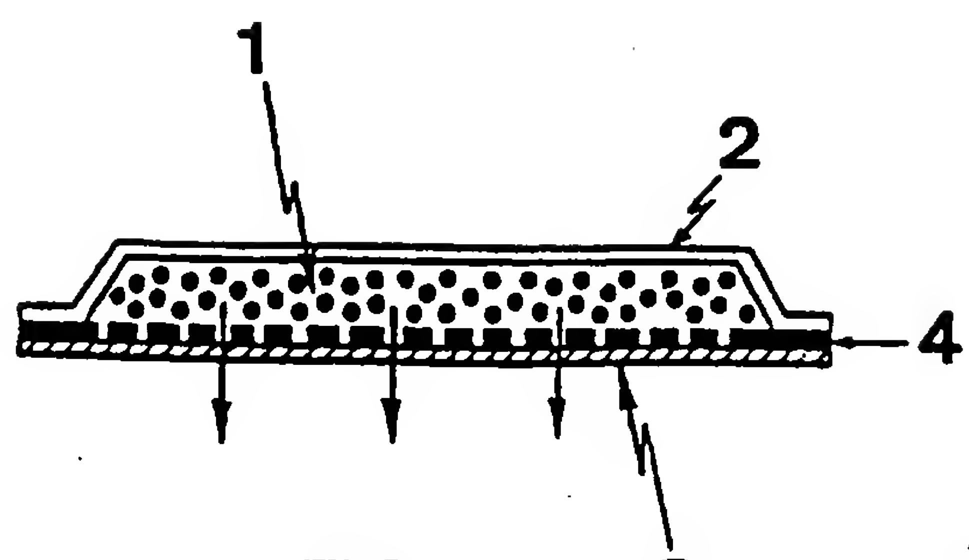

FIG. 1

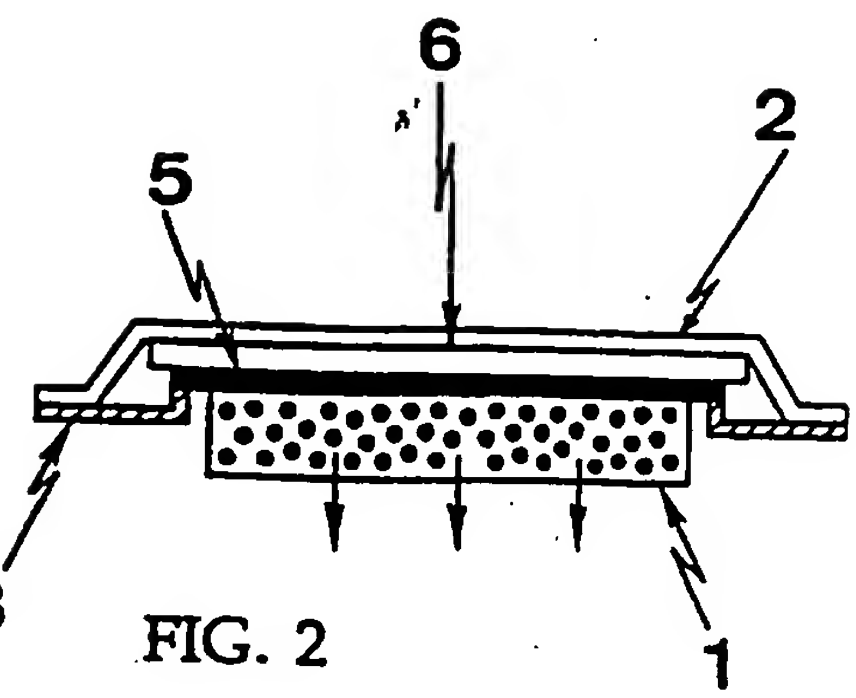

FIG. 2

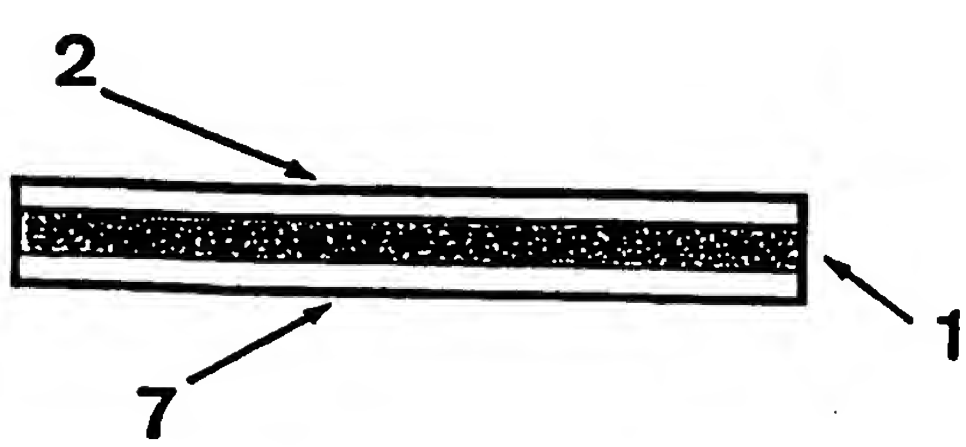

FIG. 3

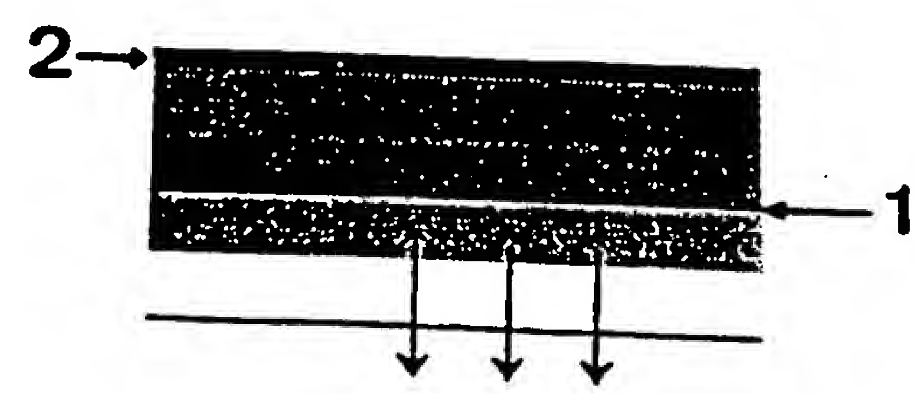

FIG. 4

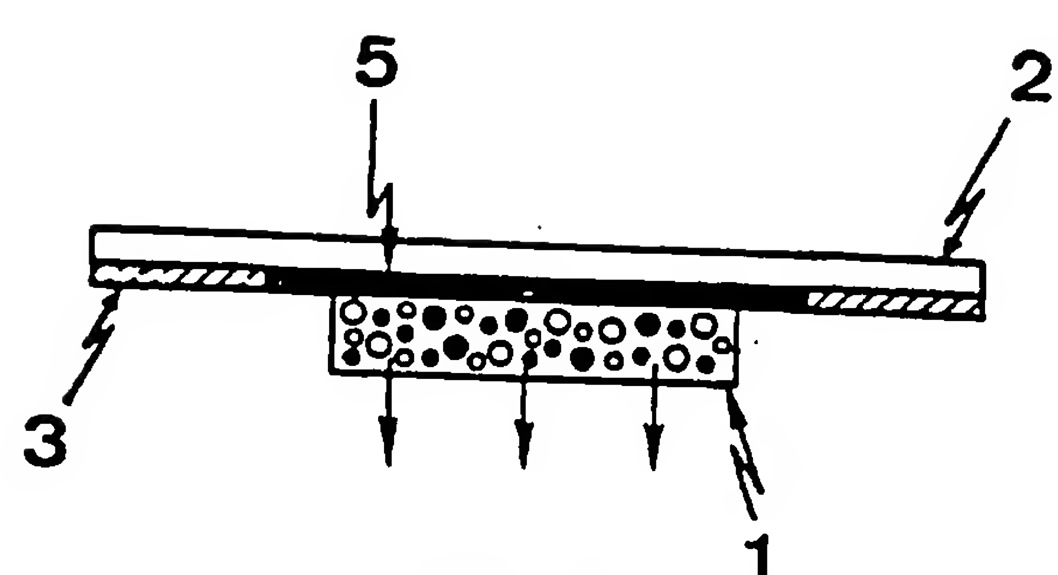

FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/01421

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 196 132 (JANSSEN PHARMACEUTICAL) 1 October 1986 cited in the application	1,19
Y	see claims 1,6-11 see page 12, line 1 - line 24 see page 13, line 10 - line 20 ---	1-18
Y	WO,A,94 06383 (RUTGERS, THE STATE UNIVERSITY OF NEW YORK) 31 March 1994 see claims 1-22 see figure 1 see page 27, line 13 ---	2-18
Y	WO,A,91 02527 (BETH ISRAEL HOSPITAL ASSOCIATION) 7 March 1991 see claims 1,5,10,11,13,14 see page 11, line 21 - page 13, line 19 ---	1-19
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 July 1996	09.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Siatou, E

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PCT/EP 96/01421

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FR,A,2 143 564 (ALZA CO) 9 February 1973 see claims 1-21 see page 8, line 25 see page 9, line 1 - line 18 ---	1-19
A	DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US AN: 120:235292, "Absorption, metabolism, and excretion of risperidone in humans" XP002008846 & Drug Metab. Dispos. 1993, 21(6), 1134-41 (G. Mannens et al) see abstract ---	1-19
A	EP,A,0 259 136 (ALZA CO) 9 March 1988 see the whole document ---	1-19
A	GB,A,2 184 016 (JONERGIN INC.) 17 June 1987 see the whole document -----	1-19

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